

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: 10/616,560
Confirmation No.: 2794
Filing Date: July 9, 2003
Examiner: Deepak R. Rao
Group Art Unit: 1624
Applicants: Mark Ledebner et al.
For: INHIBITORS OF c-JUN N-TERMINAL KINASES (JNK)
AND OTHER PROTEIN KINASES

November 1, 2007
Cambridge, Massachusetts

Mailstop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO FINAL OFFICE ACTION UNDER 37 C.F.R. §1.116

Sir:

Applicants respectfully request consideration of the reply to the May 1, 2007 Final Office Action in the above-identified application. With a three-month extension of time, a reply is due November 1, 2007. Consequently, this reply is timely submitted.

Amendments to the claims begin on page 2 of this Reply.

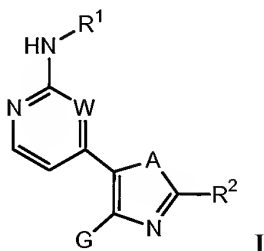
Remarks begin at page 15 of this Reply.

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AMENDMENTS TO THE CLAIMS

Please replace all prior versions and listings of claims with the amended claims as follows:

1. (Currently amended) A compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

W is nitrogen;

G is hydrogen or C₁₋₃ aliphatic;

A is -N-T_(n)-R;

R¹ is ~~selected from -T_(n)-R or~~ -T_(n)-Ar¹;

each n is independently 0 or 1;

T is a C₁₋₄ alkylidene chain wherein one methylene unit of T is optionally replaced by
-C(O)-, -C(O)O-, -C(O)NH-, -SO₂-, or -SO₂NH-;

Ar¹ is a 3-7 membered monocyclic saturated, partially saturated or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 8-10 membered bicyclic saturated, partially saturated or aromatic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein each member of Ar¹ is optionally substituted with one -Z-R³ and one to three additional groups independently selected from -R, halogen, oxo, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -NRSO₂R, -NRSO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R;

each R is independently selected from hydrogen or a C₁₋₆ aliphatic, wherein said aliphatic is optionally substituted with one to three groups independently selected from oxo, -CO₂R', -OR', -N(R')₂, -SR', -NO₂, -NR'C(O)R', -NR'C(O)N(R')₂, -

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NR'CO₂R', -C(O)R', -OC(O)R', -C(O)N(R')₂, -OC(O)N(R')₂, -S(O)R', -SO₂R', -SO₂N(R')₂, -NR'SO₂R', -NR'SO₂N(R')₂, -C(O)C(O)R', -C(O)CH₂C(O)R', halogen, or -CN, or two R bound to the same nitrogen atom are taken together with that nitrogen atom to form a five or six membered heterocyclic or heteroaryl ring having one to two additional heteroatoms independently selected from oxygen, nitrogen, or sulfur;

each R' is independently selected from hydrogen or C₁₋₆ aliphatic, wherein said aliphatic is optionally substituted with one to three groups independently selected from oxo, -CO₂H, -OH, -NH₂, -SH, -NO₂, -NHC(O)H, -NHC(O)NH₂, -NHCO₂H, -C(O)H, -OC(O)H, -C(O)NH₂, -OC(O)NH₂, -S(O)H, -SO₂H, -SO₂NH₂, -NHSO₂H, -NHSO₂NH₂, -C(O)C(O)H, -C(O)CH₂C(O)H, halogen, or -CN, or two R' bound to the same nitrogen atom are taken together with that nitrogen atom to form a five or six membered heterocyclic or heteroaryl ring optionally having one or two additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Z is a C₁₋₆ alkylidene chain wherein up to two non-adjacent methylene units of Z are optionally replaced by -C(O)-, -C(O)O-, -C(O)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)N(R)-, -N(R)N(R)C(O)-, -N(R)C(O)-, -N(R)C(O)O-, -N(R)C(O)N(R)-, -S(O)-, -SO₂-, -N(R)SO₂-, -SO₂N(R)-, -N(R)SO₂N(R)-, -O-, -S-, or -N(R)-;

R² is -Q_(n)-Ar²;

Ar² is selected from a 3-7 membered monocyclic saturated, partially saturated or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 8-10 membered bicyclic saturated, partially saturated or aromatic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein each member of Ar² is optionally substituted with 1-5 groups independently selected from -Z-R³, -R, halogen, oxo, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R;

Q is a C₁₋₃ alkylidene chain;

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R^3 is selected from $-Ar^3$, $-R$, halogen, $-NO_2$, $-CN$, $-OR$, $-SR$, $-N(R)_2$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRCO_2R$, $-C(O)R$, $-CO_2R$, $-OC(O)R$, $-C(O)N(R)_2$, $-OC(O)N(R)_2$, $-SOR$, $-SO_2R$, $-SO_2N(R)_2$, $-NRSO_2R$, $-NRSO_2N(R)_2$, $-C(O)C(O)R$, or $-C(O)CH_2C(O)R$; and

Ar^3 is a 5-6 membered saturated, partially saturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein each member of Ar^3 is optionally substituted with halogen, oxo, $-CN$, $-NO_2$, $-R'$, $-OR'$, $-N(R')_2$, $-N(R')C(O)R'$, $-N(R')C(O)N(R')_2$, $-N(R')CO_2R'$, $-C(O)R'$, $-CO_2R'$, $-OC(O)R'$, $-C(O)N(R')_2$, $-OC(O)N(R')_2$, or $-SO_2R'$;

provided that when:

~~(i) A is $-N(T)R$ and R^2 is a saturated ring, or~~

~~(ii) A is sulfur,~~

then R^1 is other than an optionally substituted phenyl.

2. (Canceled)

3. (Original) The compound according to claim 2, wherein said compound has one or more features selected from the group consisting of:

(a) R^1 is hydrogen, Ar^1 or $-T-Ar^1$ wherein T is a C_{1-4} alkylidene chain and Ar^1 is a 6-membered saturated, partially saturated, or aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each member of R^1 is optionally substituted with one $-Z-R^3$ and one to three additional groups independently selected from $-CO_2R$, $-OR$, halogen, $-NRSO_2R$, $-SO_2N(R)_2$, $-NRCON(R)_2$, $-NO_2$, or $-N(R)_2$;

(b) R^2 is Ar^2 or $-CH_2-Ar^2$ wherein Ar^2 is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, and wherein Ar^2 is optionally substituted with one to five groups independently selected from $-Z-R^3$, $-R$, halogen, $-NO_2$, $-CN$, $-OR$, $-SR$, $-N(R)_2$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRCO_2R$, $-C(O)R$, $-CO_2R$, $-C(O)N(R)_2$, $-OC(O)N(R)_2$, $-S(O)R$, $-SO_2R$, $-SO_2N(R)_2$, $-N(R)SO_2R$, $-N(R)SO_2N(R)_2$, $-C(O)C(O)R$, or $-C(O)CH_2C(O)R$; and

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(c) G is hydrogen.

4. (Original) The compound according to claim 3, wherein said compound has one or more features selected from the group consisting of:

(a) R^1 is selected from a phenyl, benzyl, pyridyl, piperidinyl, or cyclohexyl ring, wherein said ring is optionally substituted with benzyloxy, phenoxy, $-SO_2NH_2$, $-OH$, $-NO_2$, $-NH_2$, $-OMe$, $-Br$, $-Cl$, $-CO_2Me$, $-NHCO_2Me$, $-NHCO_2Et$, $-NHCON(Me)_2$, $-NHCON(Et)_2$, $-NHCOpyrrolidin-1-yl$, $-NHCOMorpholin-4-yl$, $-O-CH_2$ -phenyl, $-O(CH_2)_3OH$, $-O(CH_2)_3NH(CH_2)_2OH$, $-O(CH_2)_2NH(CH_2)_2OH$, $-O(CH_2)_3N(hydroxyethyl)(methyl)$, $-O(CH_2)_3pyrrolidin-1-yl$, $-O(CH_2)_2morpholin-4-yl$, $-O(CH_2)_3N(Me)_2$, $-O(CH_2)_3N(Et)_2$, $-O(CH_2)_3(4-hydroxyethyl piperazin-1-yl)$, $-O(CH_2)_3piperazin-1-yl$, $-O(CH_2)_3(4-hydroxymethylpiperidin-1-yl)$, $-O(CH_2)_3(4-hydroxypiperidin-1-yl)$, $-NHCO(CH_2)_3N(Me)_2$, $-NHCO(CH_2)_3NCOCH_3$, $-NHCOCH_2pyridin-2-yl$, $-NHCOCH_2(2-aminothiazol-4-yl)$, $-NHCOCH_2cyclopropyl$, $-NHCO(CH_2)_2N(Et)_2$, $-NHCO(CH_2)_2-(piperazin-2,5-dione-3-yl)$, $-NHCO_2CH_2tetrahydrofuran-2-yl$, $-NHCO_2tetrahydrofuran-2-yl$, $-NHCO_2tetrahydropyran-4-yl$, or $-NHCO_2CH_2tetrahydropyran-2-yl$;

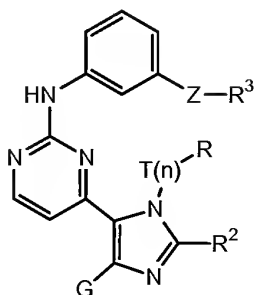
(b) R^2 is selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl, wherein R^2 is optionally substituted with phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, chloro, bromo, fluoro, trifluoromethyl, $-OH$, $-NH_2$, methyl, methoxy, or ethoxy; and

(c) G is hydrogen.

5-11. (Canceled)

12. (Previously presented) The compound according to claim 1, wherein said compound has the formula **IVa**:

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IVa

or a pharmaceutically acceptable salt thereof.

13. (Original) The compound according to claim 12, wherein said compound has one or more features selected from the group consisting of:

(a) R² is Ar² or -CH₂-Ar² wherein Ar² is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, and wherein Ar² is optionally substituted by wherein Ar² is optionally substituted with one to five groups independently selected from -Z-R³, -R, halogen, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -C(O)N(R)₂, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R;

(b) G is hydrogen;

(c) Z is a C₁₋₄ alkylidene chain wherein one methylene unit of Z is optionally replaced by -O-, -NH-, -NHC(O)-, -NHC(O)O-, -NHSO₂-, -C(O)NH-; and

(d) R³ is selected from -N(R)₂, -NHC(O)R, or Ar³ wherein Ar³ is a 5-6 membered heterocyclic or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen, or sulfur and Ar³ is optionally substituted with -R', -OR', -N(R')₂, or oxo.

14. (Original) The compound according to claim 13, wherein said compound has one or more features selected from the group consisting of:

(a) R² is selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl, wherein each member of R² is optionally substituted with phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-

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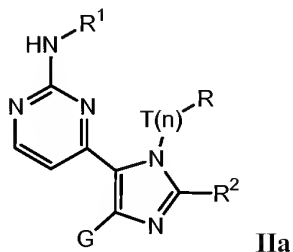
aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, chloro, bromo, fluoro, trifluoromethyl, -OH, -NH₂, methyl, methoxy, or ethoxy;

(b) G is hydrogen; and

(c) -Z-R³ is selected from -O-CH₂-phenyl, -O(CH₂)₃OH, -O(CH₂)₃NH(CH₂)₂OH, -O(CH₂)₂NH(CH₂)₂OH, -O(CH₂)₃N(hydroxyethyl)(methyl), -O(CH₂)₃pyrrolidin-1-yl, -O(CH₂)₂morpholin-4-yl, -O(CH₂)₃N(Me)₂, -O(CH₂)₃N(Et)₂, -O(CH₂)₃(4-hydroxyethyl piperazin-1-yl), -O(CH₂)₃piperazin-1-yl, -O(CH₂)₃(4-hydroxymethylpiperidin-1-yl), -O(CH₂)₃(4-hydroxypiperidin-1-yl), -NHCO(CH₂)₃N(Me)₂, -NHCO(CH₂)₃NCOCH₃, -NHCOCH₂pyridin-2-yl, -NHCOCH₂(2-aminothiazol-4-yl), -NHCOCH₂cyclopropyl, -NHCO(CH₂)₂N(Et)₂, -NHCO(CH₂)₂-(piperazin-2,5-dione-3-yl), -NHC(O)-pyrrolidin-1-yl, -NHCOMorpholin-4-yl, -NHCO₂CH₂tetrahydrofuran-2-yl, -NHCO₂tetrahydrofuran-2-yl, -NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-yl.

15-17. (Canceled)

18. (Currently amended) The compound according to claim 1 selected from one of the following compounds of formula IIa:



No. IIa-	G	-T _(n) -R	R ¹	R ²
1	H	H	4-Cl-phenyl	Ph
2	H	H	4-F-phenyl	Ph
3	H	H	3-OMe-Ph	Ph
4	H	H	3,5-(OMe) ₂ -Ph	Ph
5	H	CH ₃	4-Cl-phenyl	pyridin-3-yl
6	H	CH ₃	4-F-phenyl	pyridin-3-yl

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No. IIa-	G	-T _(n) -R	R ¹	R ²
7	H	CH ₃	Ph	pyridin-3-yl
8	H	CH ₃	3-BnO-Ph	pyridin-3-yl
9	H	CH ₃	6-Cl-pyridin-3-yl	pyridin-3-yl
10	H	CH ₂ OCH ₃	4-Cl-phenyl	Ph
11	H	CH ₂ OCH ₃	4-F-phenyl	Ph
12	H	CH ₂ OCH ₃	Ph	Ph
13	H	CH ₂ OCH ₃	4-NO ₂ -Ph	Ph
14	H	CH ₂ OCH ₃	3-OMe-Ph	Ph
15	H	CH ₂ OCH ₃	3,5-(OMe) ₂ -Ph	Ph
16	H	CH ₂ OCH ₃	3-Br-Ph	Ph
17	H	CH ₂ OCH ₃	3-BnO-Ph	Ph
18	H	CH ₃	3-OMe-Ph	pyridin-3-yl
19	H	CH ₃	3,5-(OMe) ₂ -Ph	pyridin-3-yl
20	H	CH ₃	3-Br-Ph	pyridin-3-yl
21	H	CH ₃	4-NO ₂ -Ph	pyridin-3-yl
22	H	CH ₃	3-CO ₂ CH ₃ -Ph	pyridin-3-yl
23	H	H	4-Cl-Ph	-CH ₂ -(2,6-di-Cl)-Ph
24	H	H	4-F-Ph	-CH ₂ -(2,6-di-Cl)-Ph
25	H	H	3-OMe-Ph	-CH ₂ -(2,6-di-Cl)-Ph
26	H	H	3,5-(OMe) ₂ -Ph	-CH ₂ -(2,6-di-Cl)-Ph
27	H	H	3-Br-Ph	-CH ₂ -(2,6-di-Cl)-Ph
28	H	H	Ph	-CH ₂ -(2,6-di-Cl)-Ph
29	H	H	3-BnO-Ph	-CH ₂ -(2,6-di-Cl)-Ph
30	H	H	4-NO ₂ -Ph	-CH ₂ -(2,6-di-Cl)-Ph
31	H	H	3-CO ₂ CH ₃ -Ph	-CH ₂ -(2,6-di-Cl)-Ph
32	H	H	6-Cl-pyridin-3-yl	-CH ₂ -(2,6-di-Cl)-Ph
33	H	H	cyclohexyl	-CH ₂ -(2,6-di-Cl)-Ph
34	H	CH ₂ OCH ₃	3-Cl-Ph	Ph
35	H	CH ₃	3-Cl-Ph	pyridin-3-yl
36	H	H	H	4-CO ₂ H-phenyl
37	H	H	H	4-Cl-phenyl
38	H	H	H	4-CF ₃ -phenyl
39	H	H	H	4-CH ₃ -phenyl
40	H	H	H	2-Cl-phenyl
41	H	H	H	4-OCH ₃ -phenyl
42	H	H	Ph	4-Cl-phenyl
43	H	H	Ph	4-CF ₃ -phenyl
44	H	H	Ph	4-CH ₃ -phenyl
45	H	H	CH ₂ Ph	pyridin-3-yl
46	H	H	COPh	4-Cl-phenyl
47	H	H	COPh	4-CF ₃ -phenyl
48	H	H	COPh	4-CH ₃ -phenyl
49	H	H	CONHCH ₂ Ph	4-Cl-phenyl

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No. IIa-	G	-T _(n) -R	R ¹	R ²
50	H	H	CONHCH ₂ Ph	4-CF ₃ -phenyl
51	H	H	CONHCH ₂ Ph	4-CH ₃ -phenyl
52	H	H	SO₂Me	CH₂Ph
53	H	H	Ph	thiazol-2-yl
54	H	H	cyclohexyl	piperidin-1-yl
55	H	H	cyclohexyl	4-CONHMe-phenyl
56	H	H	Ph	Ph
57	H	H	CH ₂ Ph	CH ₂ Ph
58	H	H	H	CH₂Ph
59	H	H	H	Ph
60	H	H	3-OBn-Ph	Ph
61	H	H	3-SO ₂ NH ₂ -Ph	Ph
62	H	H	3-OH-Ph	Ph
63	H	H	4-OBn-Ph	Ph
64	H	H	3-NO ₂ -Ph	3-OMe-Ph
65	H	H	3-NH ₂ -Ph	3-OMe-Ph
66	H	H	3-NO ₂ -Ph	3-OH-Ph
67	H	H	Ph	3-OBn-Ph
68	H	H	3-NO ₂ -Ph	3-OBn-Ph
69	H	H	3-NO ₂ -Ph	3-OBn-Ph
70	H	H	3-OBn-Ph	3-pyridyl
71	H	H	3-OH-Ph	3-pyridyl
72	H	H	3-NH ₂ -Ph	3-Br-Ph
73	H	H	3-NH ₂ -Ph	3-OPh-Ph
74	H	H	3-OBn-Ph	5-Br-3-pyridyl
75	H	H	Ph	3-OPh-Ph
76	H	H	3-OH-Ph	3-OBn-Ph
77	H	H	3-OH-Ph	3-OPh-Ph
78	H	H	3-OH-Ph	3-OH-Ph
79	H	H	3-OH-Ph	3-Br-Ph
80	H	H	3-OBn-Ph	3-Br-Ph
81	H	H	3-OH-Ph	3-(3-OH-Ph)-Ph
82	H	H	3-OH-Ph	3-(3-OEt-Ph)-Ph
83	H	H	3-OH-Ph	3-(3-pyridyl)-Ph
84	H	H	3-OBn-Ph	5-Ph-pyridin-3-yl
85	H	H	3-OBn-Ph	5-Br-3-pyridyl
86	H	H	3-OBn-Ph	5-Ph-3-pyridyl
87	H	H	4-OH-Ph	Ph
88	H	H	3-OH-Ph	5-Ph-pyridin-3-yl
89	H	H	3-OH-Ph	3-(3-NH ₂ -Ph)-Ph
90	H	H	3-OH-Ph	3-(3-Cl,4-F-Ph)-Ph
91	H	H	3-OH-Ph	3-(4- <i>i</i> Pr-Ph)-Ph
92	H	H	3-NO ₂ -Ph	5-Ph-pyridin-3-yl

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No. IIa-	G	-T _(n) -R	R ¹	R ²
93	H	H	3-OH-Ph	3-(3-N-Boc-pyrrol-2-yl)-Ph
94	H	H	3-NHSO ₂ Me-Ph	3-pyridyl
95	H	H	3-NHSO ₂ Et-Ph	3-pyridyl
96	H	H	3-SO ₂ NH ₂ -Ph	3-pyridyl
97	H	H	3-OH-Ph	3-(2-OH-Ph)-Ph
98	H	H	3-OH-Ph	3-(3-pyrrol-2-yl)-Ph
99	H	H	3-OH-Ph	3-(6-OMe-pyridin-2-yl)-Ph
100	H	H	3-OH-Ph	3-(5-OMe-pyridin-2-yl)-Ph
101	H	H	3-OH-Ph	3-(2,5-Me ₂ -isoxazol-4-yl)-Ph
102	H	H	3-OH-Ph	3-(pyridin-4-yl)-Ph
103	H	CH₃	H	4-CO₂H-phenyl
104	H	CH₃	H	4-Cl-phenyl
105	H	CH₃	H	4-CF₃-phenyl
106	H	CH₃	H	4-CH₃-phenyl
107	H	CH₃	H	2-Cl-phenyl
108	H	CH₃	H	4-OCH₃-phenyl
109	H	CH ₃	Ph	4-Cl-phenyl
110	H	CH ₃	Ph	4-CF ₃ -phenyl
111	H	CH ₃	Ph	4-CH ₃ -phenyl
112	H	CH ₃	CH ₂ Ph	pyridin-3-yl
113	H	CH ₃	COPh	4-Cl-phenyl
114	H	CH ₃	COPh	4-CF ₃ -phenyl
115	H	CH ₃	COPh	4-CH ₃ -phenyl
116	H	CH ₃	CONHCH ₂ Ph	4-Cl-phenyl
117	H	CH ₃	CONHCH ₂ Ph	4-CF ₃ -phenyl
118	H	CH ₃	CONHCH ₂ Ph	4-CH ₃ -phenyl
119	H	CH₃	SO₂Me	CH₂Ph
120	H	CH ₃	Ph	thiazol-2-yl
121	H	CH ₃	cyclohexyl	piperidin-1-yl
122	H	CH ₃	cyclohexyl	4-CONHMe-phenyl
123	H	CH ₃	Ph	Ph
124	H	CH ₃	CH ₂ Ph	CH ₂ Ph
125	H	CH₃	H	CH₂Ph
126	H	CH₃	H	Ph
127	H	CH ₃	3-OBn-Ph	Ph
128	H	CH ₃	3-SO ₂ NH ₂ -Ph	Ph
129	H	CH ₃	3-OH-Ph	Ph
130	H	CH ₃	4-OBn-Ph	Ph
131	H	CH ₃	3-NO ₂ -Ph	3-OMe-Ph
132	H	CH ₃	3-NH ₂ -Ph	3-OMe-Ph
133	H	CH ₃	3-NO ₂ -Ph	3-OH-Ph
134	H	CH ₃	Ph	3-OBn-Ph
135	H	CH ₃	3-NO ₂ -Ph	3-OBn-Ph

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No. IIa-	G	-T _(n) -R	R ¹	R ²
136	H	CH ₃	3-NO ₂ -Ph	3-OBn-Ph
137	H	CH ₃	3-OH-Ph	3-pyridyl
138	H	CH ₃	3-NH ₂ -Ph	3-Br-Ph
139	H	CH ₃	3-NH ₂ -Ph	3-OPh-Ph
140	H	CH ₃	3-OBn-Ph	5-Br-3-pyridyl
141	H	CH ₃	Ph	3-OPh-Ph
142	H	CH ₃	3-OH-Ph	3-OBn-Ph
143	H	CH ₃	3-OH-Ph	3-OPh-Ph
144	H	CH ₃	3-OH-Ph	3-OH-Ph
145	H	CH ₃	3-OH-Ph	3-Br-Ph
146	H	CH ₃	3-OBn-Ph	3-Br-Ph
147	H	CH ₃	3-OH-Ph	3-(3-OH-Ph)-Ph
148	H	CH ₃	3-OH-Ph	3-(3-OEt-Ph)-Ph
149	H	CH ₃	3-OH-Ph	3-(3-pyridyl)-Ph
150	H	CH ₃	3-OBn-Ph	5-Ph-pyridin-3-yl
151	H	CH ₃	3-OBn-Ph	5-Br-3-pyridyl
152	H	CH ₃	3-OBn-Ph	5-Ph-3-pyridyl
153	H	CH ₃	4-OH-Ph	Ph
154	H	CH ₃	3-OH-Ph	5-Ph-pyridin-3-yl
155	H	CH ₃	3-OH-Ph	3-(3-NH ₂ -Ph)-Ph
156	H	CH ₃	3-OH-Ph	3-(3-Cl,4-F-Ph)-Ph
157	H	CH ₃	3-OH-Ph	3-(4- <i>i</i> Pr-Ph)-Ph
158	H	CH ₃	3-NO ₂ -Ph	5-Ph-pyridin-3-yl
159	H	CH ₃	3-OH-Ph	3-(3-N-Boc-pyrrol-2-yl)-Ph
160	H	CH ₃	3-NHSO ₂ Me-Ph	3-pyridyl
161	H	CH ₃	3-NHSO ₂ Et-Ph	3-pyridyl
162	H	CH ₃	3-OMe-Ph	Ph
163	H	CH ₃	3-SO ₂ NH ₂ -Ph	3-pyridyl
164	H	CH ₃	3-OH-Ph	3-(2-OH-Ph)-Ph
165	H	CH ₃	3-OH-Ph	3-(3-pyrrol-2-yl)-Ph
166	H	CH ₃	3-OH-Ph	3-(6-OMe-pyridin-2-yl)-Ph
167	H	CH ₃	3-OH-Ph	3-(5-OMe-pyridin-2-yl)-Ph
168	H	CH ₃	3-OH-Ph	3-(2,5-Me ₂ -isoxazol-4-yl)-Ph
169	H	CH ₃	3-OH-Ph	3-(pyridin-4-yl)-Ph
170	H	CH₂OCH₃	H	4-CO₂H-phenyl
171	H	CH₂OCH₃	H	4-Cl-phenyl
172	H	CH₂OCH₃	H	4-CF₃-phenyl
173	H	CH₂OCH₃	H	4-CH₃-phenyl
174	H	CH₂OCH₃	H	2-Cl-phenyl
175	H	CH₂OCH₃	H	4-OCH₃-phenyl
176	H	CH ₂ OCH ₃	Ph	4-Cl-phenyl
177	H	CH ₂ OCH ₃	Ph	4-CF ₃ -phenyl
178	H	CH ₂ OCH ₃	Ph	4-CH ₃ -phenyl

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No. IIa-	G	-T _(n) -R	R ¹	R ²
179	H	CH ₂ OCH ₃	CH ₂ Ph	pyridin-3-yl
180	H	CH ₂ OCH ₃	COPh	4-Cl-phenyl
181	H	CH ₂ OCH ₃	COPh	4-CF ₃ -phenyl
182	H	CH ₂ OCH ₃	COPh	4-CH ₃ -phenyl
183	H	CH ₂ OCH ₃	CONHCH ₂ Ph	4-Cl-phenyl
184	H	CH ₂ OCH ₃	CONHCH ₂ Ph	4-CF ₃ -phenyl
185	H	CH ₂ OCH ₃	CONHCH ₂ Ph	4-CH ₃ -phenyl
186	H	CH₂OCH₃	SO₂Me	CH₂Ph
187	H	CH ₂ OCH ₃	Ph	thiazol-2-yl
188	H	CH ₂ OCH ₃	cyclohexyl	piperidin-1-yl
189	H	CH ₂ OCH ₃	cyclohexyl	4-CONHMe-phenyl
190	H	CH ₂ OCH ₃	CH ₂ Ph	CH ₂ Ph
191	H	CH₂OCH₃	H	CH₂Ph
192	H	CH₂OCH₃	H	Ph
193	H	CH ₂ OCH ₃	3-SO ₂ NH ₂ -Ph	Ph
194	H	CH ₂ OCH ₃	3-OH-Ph	Ph
195	H	CH ₂ OCH ₃	4-OBn-Ph	Ph
196	H	CH ₂ OCH ₃	3-NO ₂ -Ph	3-OMe-Ph
197	H	CH ₂ OCH ₃	3-NH ₂ -Ph	3-OMe-Ph
198	H	CH ₂ OCH ₃	3-NO ₂ -Ph	3-OH-Ph
199	H	CH ₂ OCH ₃	Ph	3-OBn-Ph
200	H	CH ₂ OCH ₃	3-NO ₂ -Ph	3-OBn-Ph
201	H	CH ₂ OCH ₃	3-NO ₂ -Ph	3-OBn-Ph
202	H	CH ₂ OCH ₃	3-OBn-Ph	3-pyridyl
203	H	CH ₂ OCH ₃	3-OH-Ph	3-pyridyl
204	H	CH ₂ OCH ₃	3-NH ₂ -Ph	3-Br-Ph
205	H	CH ₂ OCH ₃	3-NH ₂ -Ph	3-OPh-Ph
206	H	CH ₂ OCH ₃	3-OBn-Ph	5-Br-3-pyridyl
207	H	CH ₂ OCH ₃	Ph	3-OPh-Ph
208	H	CH ₂ OCH ₃	3-OH-Ph	3-OBn-Ph
209	H	CH ₂ OCH ₃	3-OH-Ph	3-OPh-Ph
210	H	CH ₂ OCH ₃	3-OH-Ph	3-OH-Ph
211	H	CH ₂ OCH ₃	3-OH-Ph	3-Br-Ph
212	H	CH ₂ OCH ₃	3-OBn-Ph	3-Br-Ph
213	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-OH-Ph)-Ph
214	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-OEt-Ph)-Ph
215	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-pyridyl)-Ph
216	H	CH ₂ OCH ₃	3-OBn-Ph	5-Ph-pyridin-3-yl
217	H	CH ₂ OCH ₃	3-OBn-Ph	5-Br-3-pyridyl
218	H	CH ₂ OCH ₃	3-OBn-Ph	5-Ph-3-pyridyl
219	H	CH ₂ OCH ₃	4-OH-Ph	Ph
220	H	CH ₂ OCH ₃	3-OH-Ph	5-Ph-pyridin-3-yl
221	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-NH ₂ -Ph)-Ph

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No. IIa-	G	-T _(n) -R	R ¹	R ²
222	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-Cl,4-F-Ph)-Ph
223	H	CH ₂ OCH ₃	3-OH-Ph	3-(4- <i>i</i> Pr-Ph)-Ph
224	H	CH ₂ OCH ₃	3-NO ₂ -Ph	5-Ph-pyridin-3-yl
225	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-N-Boc-pyrrol-2-yl)-Ph
226	H	CH ₂ OCH ₃	3-NHSO ₂ Me-Ph	3-pyridyl
227	H	CH ₂ OCH ₃	3-NHSO ₂ Et-Ph	3-pyridyl
228	H	CH ₂ OCH ₃	3-SO ₂ NH ₂ -Ph	3-pyridyl
229	H	CH ₂ OCH ₃	3-OH-Ph	3-(2-OH-Ph)-Ph
230	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-pyrrol-2-yl)-Ph
231	H	CH ₂ OCH ₃	3-OH-Ph	3-(6-OMe-pyridin-2-yl)-Ph
232	H	CH ₂ OCH ₃	3-OH-Ph	3-(5-OMe-pyridin-2-yl)-Ph
233	H	CH ₂ OCH ₃	3-OH-Ph	3-(2,5-Me ₂ -isoxazol-4-yl)-Ph
234	H	CH ₂ OCH ₃	3-OH-Ph	3-(pyridin-4-yl)-Ph

19. (Currently amended) A composition comprising a compound according to any one of claims [[1-4,]] 1, 3, 4, 12-14 or 18, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

20. (Previously presented) The composition according to claim 19, additionally comprising a therapeutic agent that is an agent for treating cancer.

21-22. (Canceled)

23. (Previously presented) A method of treating or lessening the severity of colon cancer, comprising the step of administering to said patient a composition according to claim 19.

24-35. (Canceled)

36. (Previously presented) The method according to claim 23, comprising the additional step of administering to said patient an additional therapeutic agent that is an anti-proliferative agent, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and

said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

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37. (Original) A composition for coating an implantable device comprising a compound according to claim 1 and a carrier suitable for coating said implantable device.

38. (Canceled)

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REMARKS

The Claim Amendments

Applicants have amended claim 1 to more particularly define variable R¹. Applicants have further amended the proviso in claim 1 to delete redundant material and to delete the recitation that A is sulfur. Support may be found in the originally-filed claim.

Applicants have amended claim 18 to recite the compounds encompassed by amended claim 1. Support may be found on pages 30-38 of the specification. Applicants have also canceled claim 2 and amended claim 19 to correct its dependency.

None of these amendments adds new matter. Further, the amended claims do not require a new search. Their entry is requested.

Applicants reserve the right to pursue the canceled subject matter in this application or in future continuing or divisional applications.

The Response

The Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-4, 12-14, 18-20, 23 and 36-37 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants have amended the claims to obviate these rejections. Specifically, the Examiner contends that the recitation “A is sulfur” in the proviso of claim 1 lacks antecedent basis in amended claim 1. Applicants have amended claim 1 to delete this recitation.

Duplicate Claims

The Examiner states that should claim 1 be found allowable, claim 2 will be objected to under 37 C.F.R. §1.75 as being a substantial duplicate thereof.

Applicants have canceled claim 2, thereby obviating this objection.

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The Rejections Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-2, 19-20, 23-25 and 37 as being obvious over WO 02/083111 (hereafter “the ‘111 application”). The Examiner states that the ‘111 application teaches imidazolyl compounds that are structurally analogous to the instantly claimed compounds. The Examiner acknowledges that the instant compounds differ from the reference compounds by having the pyrimidine attached through a position different from the reference compounds, but contends that it would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are positional isomers of the reference compounds. The Examiner alleges that applicants’ arguments are not persuasive because the ‘111 application teaches a use for the compounds as therapeutic agents in the treatment of hypertension, which is sufficient to one of ordinary skill to make the claimed compounds because similar compounds would be expected to share similar properties and to have the same use as taught for the reference compounds, i.e., as therapeutic agents. The Examiner also argues that “[a]pplicants must prove that their compounds possess a property that the prior art compounds do not possess,” and further contends that *In re Best*, 562 F.2d 1252 (CCPA 1977) stands for the proposition “[t]he discovery of additional use not disclosed in the reference does not make otherwise obvious compounds unobvious.” Applicants traverse.

First, the Examiner states that the ‘111 application teaches imidazolyl compounds that are structurally analogous to the instantly claimed compounds. This is not the case. The ‘111 application teaches a single imidazolyl pyrimidineamine compound (compound 100) out of more than 640 compounds. Further, although the ‘111 application provides biological data for over 160 compounds, it provides no biological data for compound 100 and fails to single out compound 100 in any way. Given the lack of biological data and the fact that the application teaches only one imidazolyl pyrimidineamine, one having ordinary skill in the art could reasonably infer that compound 100 was ineffective as a large conductance calcium-activated potassium channel opener. Thus, given the large number of compounds exemplified and the lack of data for compound 100, there is no motivation provided by the ‘111 application itself or known to one having ordinary skill

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in the art that would lead an ordinary artisan to choose compound 100 and modify it as suggested by the Examiner. See *Takeda v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007), which held that a compound is not obvious when the prior art teaches a broad selection of compounds, any one of which could have been selected as a lead compound for further investigation, and where there is evidence that the closest prior art compound exhibits negative properties.

Second, the Examiner's reliance on *In re Best*, 562 F.2d 1252 (CCPA 1977), is inapposite. In *Best*, the CCPA held that "[w]here, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove the prior art products do not necessarily or inherently possess the characteristics of his claimed product." See *Best*, 562 F.2d at 1255. In this case, the claimed compounds are not identical or substantially identical to compound 100 or to any other compound in the '111 application, which is acknowledged by the Examiner. At most, *Best* stands only for the proposition that the discovery of an additional characteristic not disclosed in the reference does not make an otherwise identical or substantially identical compound unobvious. Thus, *Best* does not require that applicants must prove that the claimed compounds possess a property that the prior art compounds do not possess because the claimed compounds are not identical or substantially identical to any compound in the '111 application.

Third, the Examiner is incorrect in stating that applicants have not shown that their compounds possess a property that the prior art compounds do not possess. In fact, applicants have provided ample data that the claimed compounds are JNK, Src, Lck and Aurora-2 kinase inhibitors that are useful for treating a variety of diseases, including cancer. Nothing in the '111 application teaches or suggests such a property.

Fourth, as discussed previously in applicants' August 10, 2006 response, the claimed compounds are not obvious in light of the '111 application because applicants teach that the claimed compounds have nonobvious and unexpected properties, which is that they inhibit JNK, Src, Lck and Aurora-2 kinases, which are neither taught nor suggested by the '111 application. As discussed previously, the '111 application

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contends only that the compounds could be used as large conductance calcium-activated potassium channel openers (see, e.g., page 1, lines 8-11 of the ‘111 application), and contends only that the compounds could be used for treating disorders such as pollakiuria, urinary incontinence, cerebral infarction and subarachnoid hemorrhage (see, e.g., page 1, lines 11-13 of the ‘111 application). One having ordinary skill in the art would have had no expectation of success that making “isomeric compounds” of the ‘111 application would result in protein kinase inhibitors useful in treating cancer given that the ‘111 application is concerned only with calcium-activated potassium channel openers. Thus, contrary to the Examiner’s assertion, the teachings of the ‘111 application do not provide any reason to one having ordinary skill in the art to make the instantly-claimed compounds because the instantly-claimed compounds have different molecular targets, different mechanisms of action and different medical applications than that which is disclosed in the ‘111 application.

Finally, the Examiner’s reliance on *In re Finley*, 81 USPQ 383 (CCPA 1949), *In re Norris*, 84 USPQ 458 (CCPA 1950) and *In re Dillon*, 919 F.2d 688 (CAFC 1990) is misplaced. *Norris*, *Finley* and *Dillon* all relate to claims to compounds of use in the chemical arts,¹ not in the pharmaceutical arts. While it may be the case in certain circumstances that one of ordinary skill in the chemical arts would expect that structurally similar compounds, such as positional isomers, would have similar *physicochemical* properties, it is not the case that one of ordinary skill in the pharmaceutical arts would expect such similarities in the context of *biological activities*. In fact, in the field of pharmaceutical chemistry, it is well known that subtle structural changes can have significant effects on biological activity. Thus, the mere fact the ‘111 application provides a single compound that is a positional isomer of the claimed compounds does not render the claimed invention obvious. For these reasons, applicants request that the Examiner withdraw his rejection of the pending claims under 35 U.S.C. §103(a) as being obvious over the ‘111 application.

¹ *Norris* relates to a chemical intermediate, *Finley* relates to a lubricant additive, and *Dillon* relates to a hydrocarbon fuel additive.

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Conclusion

Applicants request that the Examiner enter the above amendments, consider the accompanying arguments, and allow the claims to pass to issue. Should the Examiner deem expedient a telephone discussion to further the prosecution of the above application, applicants request that the Examiner contact the undersigned at his convenience.

Respectfully submitted,

/Karen E. Brown/
Karen E. Brown
Reg. No. 43,866
Attorney for Applicants
c/o Vertex Pharmaceuticals Incorporated
130 Waverly Street
Cambridge, Massachusetts 02139
Tel: (617) 444-6168
Fax: (617) 444-6483